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(54) **Title**: FLUID LEVEL INDICATOR DETERMINATION

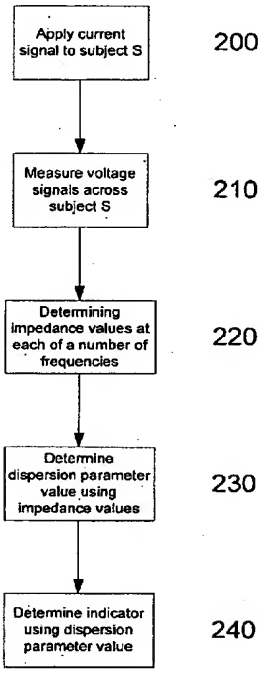

Fig. 2

(57) **Abstract**: A method for use in analysing impedance measurements performed on a subject, the method including, in a processing system, determining at least one impedance value at each of a number of frequencies, each impedance value representing the impedance of a segment of the subject, determining a dispersion parameter value indicative of a dispersion of the impedance values and, determining an indicator based at least in part on the dispersion parameter value.

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FLUID LEVEL INDICATOR DETERMINATION

Background of the Invention

The present invention relates to a method and apparatus for use in analysing impedance measurements performed on a subject, and in particular to a method and apparatus for determining an indicator using a dispersion parameter, to thereby allow the indicator to be used in diagnosing the presence, absence or degree of oedema.

Description of the Prior Art

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that the prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

One existing technique for determining biological parameters relating to a subject, such as fluid levels, involves the use of bioelectrical impedance. This involves measuring the electrical impedance of a subject's body using a series of electrodes placed on the skin surface. Changes in electrical impedance at the body's surface are used to determine parameters, such as changes in fluid levels, associated with the cardiac cycle or oedema, or other conditions which affect body habitus.

Lymphoedema is a condition characterised by excess protein and oedema in the tissues as a result of reduced lymphatic transport capacity and/or reduced tissue proteolytic capacity in the presence of a normal lymphatic load. Acquired, or secondary lymphoedema, is caused by damaged or blocked lymphatic vessels. The commonest inciting events are surgery and/or radiotherapy. However, onset of lymphoedema is unpredictable and may develop within days of its cause or at any time during a period of many years after that cause.

WO00/79255 describes a method of detection of oedema by measuring bioelectrical impedance at two different anatomical regions in the same subject at a single low frequency

alternating current. The two measurements are analysed to obtain an indication of the presence of tissue oedema by comparing with data obtained from a normal population.

WO2005/122888 describes a method of detecting tissue oedema in a subject. The method includes determining a measured impedance for first and second body segments. An index indicative of a ratio of the extra-cellular to intra-cellular fluid is then calculated for each body segment, with these being used to determine an index ratio based on the index for the first and second body segments. The index ratio can in turn be used to determine the presence, absence or degree of tissue oedema, for example by comparing the index ratio to a reference or previously determined index ratios.

WO2008/138602 describes a method for use in analysing impedance measurements performed on a subject, the method including, in a processing system determining at least one impedance value, representing the impedance of at least a segment of the subject, determining an indicator indicative of a subject parameter using the at least one impedance value and a reference and displaying a representation of the indicator.

Summary of the Present Invention

It is an object of the present invention to substantially overcome, or at least ameliorate, one or more disadvantages of existing arrangements.

In a first broad form the present invention seeks to provide a method for use in analysing impedance measurements performed on a subject, the method including, in a processing system:

a) determining at least one impedance value at each of a number of frequencies, each impedance value representing the impedance of a segment of the subject;
b) determining a dispersion parameter value indicative of a dispersion of the impedance values; and,
c) determining an indicator based at least in part on the dispersion parameter value.

Typically the method includes, in the processing system:

a) determining first and second dispersion parameter values for first and second body segments respectively; and,

b) determining the indicator using the first and second dispersion parameter values.

Typically the first body segment is an affected body segment and the second body segment is an unaffected body segment.

Typically at least one of the body segments is a dominant limb and the other body segment is a non-dominant limb.

Typically the first body segment is a different body segment to the second body segment.

Typically the method includes, in the processing system:

a) determining a predicted dispersion parameter value for the first body segment using the second dispersion parameter value;

b) determining the indicator using the first and predicted dispersion parameter values.

Typically predicted dispersion parameter value is determined to take into account at least one of:

a) limb dominance; and,

b) differences in limb types.

Typically the method includes, in the processing system, determining a predicted dispersion parameter value using at least one reference value derived from a reference normal population.

Typically the reference normal population is selected based on at least one of:

a) limb dominance;

b) differences in limb types;

c) ethnicity;

d) age;

e) gender;

f) weight; and,

g) height.

Typically the at least one reference value is determined based on a linear regression of first and second dispersion parameter values measured for the reference normal population.

Typically the method includes, in the processing system, determining the predicted dispersion parameter value using an equation of the form:

$$DP_p = aDP_2 + K$$

where: DP_2 is the second dispersion parameter value

DP_p is the predicted dispersion parameter value

a is a multiplier reference value determined based on a relationship between first and second dispersion parameter values in a reference population

K is a constant reference value determined based on a relationship between first and second dispersion parameter values in a reference population

Typically, for a male subject, the predicted value for a leg segment based on second dispersion parameters for an arm segment is based on:

a) a value of a in the range 0.15 to 0.022; and,

b) a value of K in the range 0.62 to 0.72.

Typically, for a female subject, the predicted value for a leg segment based on second dispersion parameters for an arm segment is based on:

a) a value of a in the range 0.44 to 0.41; and,

b) a value of K in the range 0.43 to 0.46.

Typically the method includes, in the processing system, determining the indicator using the equation:

$$Ind = \frac{sf \times \left(DP_p - DP_1\right)}{3SE}$$

where: Ind is the indicator

DP_1 is a dispersion parameter value determined for the body segment

DP_p is a predicted dispersion parameter value for the body segment

sf is a scaling factor

SE is a standard error determined based on dispersion parameter values in a reference population

Typically the method includes, in the processing system, determining the indicator using the equation:

$$Ind = \frac{sf \times (DP_\mu - DP_1)}{3SE}$$

where:

DP_μ is the mean dispersion parameter value for a reference normal population

DP_1 is a dispersion parameter value determined for the body segment

sf is a scaling factor

SE is a standard error determined for the dispersion parameter values for the reference population

Typically the scaling factor is selected so that a threshold value indicative of the presence or absence of oedema is an integer value.

Typically the method includes, in the processing system, determining the indicator based on the equation:

$$Ind = sf(DP_2 - DP_1)$$

where:

Ind is the indicator

DP_1 is a first dispersion parameter value for a first body segment

DP_2 is a second dispersion parameter value for a second body segment

sf is a scaling factor

Typically the dispersion parameter value is indicative of the distribution of impedance measurements for the respective body segment.

Typically the dispersion parameter is based on the value of at least one of:

$$DP = \frac{(R_0 - R_\infty)}{X_c}$$

$$DP = \frac{X_c}{(R_0 - R_\infty)}$$

$$DP = \frac{(R_\infty - R_0)}{X_c}$$

$$DP = \frac{X_c}{(R_\infty - R_0)}$$

where: R_∞ = impedance at infinite applied frequency;

R_0 = impedance at zero applied frequency;

X_c = reactance at the centre of the circle.

Typically the dispersion parameter is based on the value of:

$$\alpha = \frac{2}{\pi} a\tan\frac{(R_0 - R_\infty)}{2|X_c|}$$

Typically the indicator is at least one of:

a) an oedema indicator for use in assessing a presence, absence or degree of oedema in the subject.

b) a hydration indicator for use in assessing hydration levels in a subject.

Typically the method includes, in the processing system, displaying a representation of the indicator.

Typically representation of the indicator includes a linear scale including:

a) a linear indicator;

b) a scale; and,

c) a pointer, the pointer being positioned on the scale in accordance with the indicator.

Typically the method includes, in the processing system, displaying a representation including an indication of a change in indicator value from at least one of a previous indicator value and a baseline indicator value.

Typically the method includes, in the processing system:

a) determining at least one threshold using a reference; and,

b) displaying the threshold as part of the representation.

Typically the method includes, in the processing system:

a) determining two thresholds using a reference; and,

b) displaying the thresholds on the representation, the thresholds being indicative of a normal range.

Typically the method includes, in the processing system, displaying, on the representation, at least one of:

a) a normal range;

b) an intervention range;

c) a hydration range; and,

d) an oedema range.

Typically the method includes in the processing system, causing one or more impedance measurements to be performed.

Typically the method includes, in the processing system:

a) causing at least one excitation signal to be applied to the subject;

b) determining at least one signal measured across the subject; and,

c) determining at least one impedance value using an indication of the excitation signal and the signal measured across the subject.

Typically the method includes, in the processing system:

a) controlling a signal generator to thereby cause the at least one excitation signals to be applied to the subject; and,

b) determining the at least one signal measured across the subject using a sensor.

In a second broad form the present invention seeks to provide apparatus for use in analysing impedance measurements performed on a subject, the apparatus including a processing system for:

a) determining at least one impedance value at each of a number of frequencies, each impedance value representing the impedance of a segment of the subject;

b) determining a dispersion parameter value indicative of a dispersion of the impedance values; and,

c) determining an indicator based at least in part on the dispersion parameter value.

Typically the apparatus includes:

a) a signal generator for applying one or more electrical signals to the subject using a first set of electrodes;

b) a sensor for measuring electrical signals across a second set of electrodes applied to the subject; and,

c) a controller for:

i) controlling the signal generator; and,

ii) determining the indication of the measured electrical signals.

Typically the controller includes the processing system.

Typically the processing system includes the controller.

In a third broad form the present invention seeks to provide a method for use diagnosing the presence, absence or degree of oedema in a subject by using impedance measurements performed on the subject, the method including, in a processing system:

a) determining at least one impedance value at each of a number of frequencies, each impedance value representing the impedance of a segment of the subject;

b) determining a dispersion parameter value indicative of a dispersion of the impedance values;

c) determining an indicator based at least in part on the dispersion parameter value; and,

d) displaying a representation of the indicator, to thereby allow the presence, absence or degree of oedema in the subject to be assessed.

It will be appreciated that the broad forms of the invention may be used individually or in combination, and may be used for diagnosis of the presence, absence or degree of a range of conditions and illnesses, including, but not limited to oedema, lymphoedema, body composition and the like.

Brief Description of the Drawings

An example of the present invention will now be described with reference to the accompanying drawings, in which: -

Figure 1 is a schematic of an example of impedance determination apparatus;

Figure 2 is a flowchart of an example of a process for determining an indicator;

Figure 3A is a schematic of an example of a theoretical equivalent circuit for biological tissue;

Figure 3B is an example of a locus of impedance known as a Wessel plot;

Figure 4 is a flowchart of an example of a process for determining an oedema indicator for limb oedema;

Figures 5A and 5B are diagrams of examples of electrode positions for use in measuring limb impedances;

Figures 5C and 5D are schematic diagrams of examples of electrode positions for use in measuring limb impedances;

Figure 6A to 6C are schematic diagrams of first examples of representations of oedema indicators;

Figure 7 are graphs of examples of the relationship of parameters between like limbs and dislike limbs; and,

Figure 8 is a graph of example measurements of leg α and arm α for healthy female dominant arms and legs.

Detailed Description of the Preferred Embodiments

An example of apparatus suitable for performing an analysis of a subject's bioelectric impedance will now be described with reference to Figure 1.

As shown the apparatus includes a measuring device 100 including a processing system 102, connected to one or more signal generators 117A, 117B, via respective first leads 123A, 123B, and to one or more sensors 118A, 118B, via respective second leads 125A, 125B. The connection may be via a switching device, such as a multiplexer, although this is not essential.

In use, the signal generators 117A, 117B are coupled to two first electrodes 113A, 113B, which therefore act as drive electrodes to allow signals to be applied to the subject *S*, whilst the one or more sensors 118A, 118B are coupled to the second electrodes 115A, 115B, which act as sense electrodes, allowing signals across the subject *S* to be sensed.

The signal generators 117A, 117B and the sensors 118A, 118B may be provided at any position between the processing system 102 and the electrodes 113A, 113B, 115A, 115B, and may be integrated into the measuring device 100. However, in one example, the signal generators 117A, 117B and the sensors 118A, 118B are integrated into an electrode system, or another unit provided near the subject *S*, with the leads 123A, 123B, 125A, 125B connecting the signal generators 117A, 117B and the sensors 118A, 118B to the processing system 102.

It will be appreciated that the above described system is a two channel device, used to perform a classical four-terminal impedance measurement, with each channel being designated by the suffixes A, B respectively. The use of a two channel device is for the purpose of example only, and multiple channel devices can alternatively be used to allow multiple body segments to be measured without requiring reattachment of electrodes. An example of such a device is described in copending patent application number WO2009059351.

An optional external interface 103 can be used to couple the measuring device 100, via wired, wireless or network connections, to one or more peripheral devices 104, such as an external database or computer system, barcode scanner, or the like. The processing system 102 will also typically include an I/O device 105, which may be of any suitable form such as a touch screen, a keypad and display, or the like.

In use, the processing system 102 is adapted to generate control signals, which cause the signal generators 117A, 117B to generate one or more alternating signals, such as voltage or current signals of an appropriate waveform, which can be applied to a subject *S*, via the first electrodes 113A, 113B. The sensors 118A, 118B then determine the voltage across or current through the subject *S*, using the second electrodes 115A, 115B and transfer appropriate signals to the processing system 102.

Accordingly, it will be appreciated that the processing system 102 may be any form of processing system which is suitable for generating appropriate control signals and at least partially interpreting the measured signals to thereby determine the subject's bioelectrical impedance, and optionally determine other information such as relative fluid levels, or the presence, absence or degree of conditions, such as oedema, lymphoedema, measures of body composition, cardiac function, or the like.

The processing system 102 may therefore be a suitably programmed computer system, such as a laptop, desktop, PDA, smart phone or the like. Alternatively the processing system 102 may be formed from specialised hardware, such as an FPGA (field programmable gate array), or a combination of a programmed computer system and specialised hardware, or the like, as will be described in more detail below.

In use, the first electrodes 113A, 113B are positioned on the subject to allow one or more signals to be injected into the subject *S*. The location of the first electrodes will depend on the segment of the subject *S* under study. Thus, for example, the first electrodes 113A, 113B can be placed on the thoracic and neck region of the subject *S* to allow the impedance of the chest cavity to be determined for use in cardiac function analysis. Alternatively, positioning electrodes on the wrist and ankles of a subject allows the impedance of limbs and/or the entire body to be determined, for use in oedema analysis, or the like.

Once the electrodes are positioned, one or more alternating signals are applied to the subject *S*, via the first leads 123A, 123B and the first electrodes 113A, 113B. The nature of the alternating signal will vary depending on the nature of the measuring device and the subsequent analysis being performed.

For example, the system can use Bioimpedance Spectroscopy (BIS) in which impedance measurements are performed at each of a number of frequencies ranging from very low frequencies (4 kHz) to higher frequencies (1000 kHz), and can use as many as 256 or more different frequencies within this range. Such measurements can be performed by applying a signal which is a superposition of plurality of frequencies simultaneously, or a number of alternating signals at different frequencies sequentially, depending on the preferred implementation. The frequency or frequency range of the applied signals may also depend on the analysis being performed.

In one example, the applied signal is generated by a voltage generator, which applies an alternating voltage to the subject *S*, although alternatively current signals may be applied. In one example, the voltage source is typically symmetrically arranged, with each of the signal generators 117A, 117B being independently controllable, to allow the signal voltage across the subject to be varied.

A voltage difference and/or current is measured between the second electrodes 115A, 115B. In one example, the voltage is measured differentially, meaning that each sensor 118A, 118B is used to measure the voltage at each second electrode 115A, 115B and therefore need only measure half of the voltage as compared to a single ended system.

The acquired signal and the measured signal will be a superposition of voltages generated by the human body, such as the ECG (electrocardiogram), voltages generated by the applied signal, and other signals caused by environmental electromagnetic interference. Accordingly, filtering or other suitable analysis may be employed to remove unwanted components.

The acquired signal is typically demodulated to obtain the impedance of the system at the applied frequencies. One suitable method for demodulation of superposed frequencies is to use a Fast Fourier Transform (FFT) algorithm to transform the time domain data to the frequency domain. This is typically used when the applied current signal is a superposition of applied frequencies. Another technique not requiring windowing of the measured signal is a sliding window FFT.

In the event that the applied current signals are formed from a sweep of different frequencies, then it is more typical to use a signal processing technique such as multiplying the measured signal with a reference sine wave and cosine wave derived from the signal generator, or with measured sine and cosine waves, and integrating over a whole number of cycles. This process, known variously as quadrature demodulation or synchronous detection, rejects all uncorrelated or asynchronous signals and significantly reduces random noise.

Other suitable digital and analogue demodulation techniques will be known to persons skilled in the field.

In the case of BIS, impedance or admittance measurements are determined from the signals at each frequency by comparing the recorded voltage and the current through the subject. The demodulation algorithm can then produce amplitude and phase signals at each frequency, allowing an impedance value at each frequency to be determined.

As part of the above described process, the distance between the second electrodes 115A, 115B may be measured and recorded. Similarly, other parameters relating to the subject may be recorded, such as the height, weight, age, sex, health status, any interventions and the date and time on which they occurred. Other information, such as current medication, may also be recorded. This can then be used in performing further analysis of the impedance measurements, so as to allow determination of the presence, absence or degree of oedema, to assess body composition, or the like.

The accuracy of the measurement of impedance can be subject to a number of external factors. These can include, for example, the effect of capacitive coupling between the subject and the surrounding environment, the leads and the subject, the electrodes, or the like, which will vary based on factors such as lead construction, lead configuration, subject position, or the like. Additionally, there are typically variations in the impedance of the electrical connection between the electrode surface and the skin (known as the "electrode impedance"), which can depend on factors such as skin moisture levels, melatonin levels, or the like. A further source of error is the presence of inductive coupling between different electrical conductors within the leads, or between the leads themselves.

Such external factors can lead to inaccuracies in the measurement process and subsequent analysis and accordingly, it is desirable to be able to reduce the impact of external factors on the measurement process.

One form of inaccuracy that can arise is caused by the voltages across the subject being unsymmetrical, a situation referred to as an "imbalance". Such a situation results in a significant signal voltage at the subject's body centre, which in turn results in stray currents arising from parasitic capacitances between the subject's torso and the support surface on which the subject is provided.

The presence of an imbalance, where the voltage across the subject is not symmetrical with respect to the effective centre of the subject, leads to a "common mode" signal, which is effectively a measure of the signal at the subject S that is unrelated to the subject's impedance.

To help reduce this effect, it is therefore desirable for signals to be applied to the subject S that they result in a symmetrical voltage about the subject's body centre. As a result, a reference voltage within the subject S, which is equal to a reference voltage of the measurement apparatus, will be close to the effective body centre of the subject, as considered relative to the electrode placement. As the measuring device reference voltage is typically ground, this results in the body centre of the subject S being as close to ground as possible, which minimises the overall signal magnitude across the subject's torso, thereby minimising stray currents.

In one example, a symmetrical voltage about the sensing electrodes can be achieved by using a symmetrical voltage source, such as a differential bidirectional voltage drive scheme, which applies a symmetrical voltage to each of the drive electrodes 113A, 113B. However, this is not always effective if the contact impedances for the two drive electrodes 113A, 113B are unmatched, or if the impedance of the subject S varies along the length of the subject S, which is typical in a practical environment.

In one example, the apparatus overcomes this by adjusting the differential voltage drive signals applied to each of the drive electrodes 113A, 113B, to compensate for the different

electrode impedances, and thereby restore the desired symmetry of the voltages across the subject *S*. This process is referred to herein as *balancing* and in one example, helps reduce the magnitude of the common mode signal, and hence reduce current losses caused by parasitic capacitances associated with the subject.

The degree of imbalance, and hence the amount of balancing required, can be determined by monitoring the signals at the sense electrodes 115A, 115B, and then using these signals to control the signal applied to the subject via the drive electrodes 113A, 113B. In particular, the degree of imbalance can be calculated by determining an additive voltage from the voltages detected at the sense electrodes 115A, 115B.

In one example process, the voltages sensed at each of the sense electrodes 115A, 115B are used to calculate a first voltage, which is achieved by combining or adding the measured voltages. Thus, the first voltage can be an additive voltage (commonly referred to as a common mode voltage or signal) which can be determined using a differential amplifier.

In this regard, a differential amplifier is typically used to combine two sensed voltage signals V_a, V_b, to determine a second voltage, which in one example is a voltage differential V_a-V_b across the points of interest on the subject *S*. The voltage differential is used in conjunction with a measurement of the current flow through the subject to derive impedance values. However, differential amplifiers typically also provide a "common mode" signal $(V_a+V_b)/2$, which is a measure of the common mode signal.

Whilst differential amplifiers include a common mode rejection capability, this is generally of only finite effect and typically reduces in effectiveness at higher frequencies, so a large common mode signal will produce an error signal superimposed on the differential signal.

The error caused by common mode signals can be minimised by calibration of each sensing channel. In the ideal case where both inputs of a differential amplifier are perfectly matched in gain and phase characteristics and behave linearly with signal amplitude, the common mode error will be zero. In one example, the two sensing channels of the differential amplifier are digitised before differential processing. It is therefore straightforward to apply

calibration factors independently to each channel to allow the characteristics to be matched to a high degree of accuracy, thereby achieving a low common mode error.

Accordingly, by determining the common mode signal, the applied voltage signals can be adjusted, for example by adjusting the relative magnitude and/or phase of the applied signals, to thereby minimise the common mode signal and substantially eliminate any imbalance. An example of this process is described in more detail in copending patent application number WO2009059351.

An example of the operation of the apparatus in analysing impedance measurements will now be described with reference to Figure 2.

In one example, at step 200 the processing system 102 causes a current signal to be applied to the subject S, with the induced voltage across the subject S being measured at step 210, with signals representing the measured voltage and the applied current being returned to the processing system 102 for analysis.

When the process is being used to determine an oedema indicator, this is typically performed for at least a segment of the subject S that is suspected of being susceptible to oedema, and may also be repeated for a separate healthy segment of the subject. Thus, for example, in the case of limb oedema, this is typically performed on the affected or "at risk" limb (hereinafter generally referred to as the "affected" limb), and a limb that is deemed "not at risk" of oedema (hereinafter generally referred to as the "unaffected" limb).

It will be appreciated that the application of the current and voltage signals may be controlled by a separate processing system that is used in performing the analysis to derive an indicator, and that the use of a single processing system is for the purpose of example only.

At step 220, measured voltage and current signals are used by the processing system 102 to determine impedance values at each of a number of applied frequencies. In one example, this includes first impedance values representing the impedance of the unaffected limb and second impedance values representing the impedance of the affected limb.

At step 230, the one or more impedance values are used by the processing system 102, to determine a dispersion parameter value. In one example, first and second dispersion parameter values of affected and unaffected limbs may be determined.

The nature of the dispersion parameter can vary, but in general this represents a distribution of the impedance measurements about an ideal model.

In one example, the dispersion parameter DP can be given by or based on the value:

$$DP = \frac{X_c}{(R_0 - R_\infty)} \tag{1}$$

where: R_∞ = impedance at infinite applied frequency;

R_0 = impedance at zero applied frequency;

X_c = reactance at the centre of the circle.

It should be noted that the value of X_c will be negative, due to it's position below the circle, and this can lead to the value of the dispersion parameter being negative. However, it will be appreciated that alternative formulations may also be used, such as those set out below, and accordingly, the dispersion parameter can be arranged to have either a positive or negative value, as desired:

$$DP = \frac{(R_0 - R_\infty)}{X_c} \tag{1A}$$

$$DP = \frac{(R_\infty - R_0)}{X_c} \tag{1B}$$

$$DP = \frac{X_c}{(R_\infty - R_0)} \tag{1C}$$

The alternative formulations can be used to ensure that the value of the dispersion parameter increases in the event that the subject has oedema, although this is not essential and any suitable formulation may be selected.

In one particular example, the dispersion parameter DP value is given by a value α:

$$\alpha = \frac{2}{\pi}\arctan\frac{(R_0 - R_\infty)}{2|X_c|} \quad (2)$$

In this regard, Figure 3A is an example of an equivalent circuit that effectively models the electrical behaviour of biological tissue. The equivalent circuit has two branches that represent current flow through extracellular fluid and intracellular fluid, respectively. The extracellular fluid component of biological impedance is represented by an extracellular resistance R_e, whilst the intracellular fluid component is represented by an intracellular resistance R_i and a capacitance C representative of the cell membranes.

The relative magnitudes of the extracellular and intracellular components of impedance of an alternating current (AC) are frequency dependent. At zero frequency the capacitor acts as a perfect insulator and all current flows through the extracellular fluid, hence the resistance at zero frequency, R_0, equals the extracellular resistance R_e. At infinite frequency the capacitor acts as a perfect conductor and the current passes through the parallel resistive combination. The resistance at infinite frequency R_∞ is given by:

$$R_\infty = \frac{R_e R_i}{R_e + R_i} \quad (3)$$

Accordingly, the impedance of the equivalent circuit of Figure 3A at an angular frequency ω, where ω=2π*frequency, is given by:

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)} \quad (4)$$

where: R_∞= impedance at infinite applied frequency

R_0 = impedance at zero applied frequency = R_e and,

τ is the time constant of the capacitive circuit.

However, the above represents an idealised situation which does not take into account the fact that the cell membrane is an imperfect capacitor. Taking this into account leads to a modified model in which:

$$Z = R_\infty + \frac{R_0 - R_\infty}{1 + (j\omega\tau)^\alpha} \qquad (5)$$

where: α has a value between 0 and 1 and can be thought of as an indicator of the deviation of a real system from the ideal model.

An example of the typical multi-frequency impedance response is shown in Figure 3B. As frequency increases, the reactance increases to a peak and then decreases while the resistance continually decreases. This results in a circular locus with the centre of the circle below the x axis, as shown.

The α parameter is related to the depression of the Cole plot below the zero reactance axis. The value of α is indicative of the deviation from the ideal Cole equation (4) and is closely related to the spectral width of the distribution of relaxation times. This dispersion may be due to molecular interactions, cellular interactions, anisotropy and cell size as described in Grimnes, S. and O. G. Martinsen (2000). Bioimpedance and Bioelectricity Basics, Academic Press.

As described above, the value of the impedance parameter R_0 is closely related to extra-cellular fluid levels while the impedance parameter value R_∞ is closely related to the total body fluid levels. Accordingly, (R_0 - R_∞) is closely related to the intra-cellular fluid levels.

The reactance X_c is the reactance X at the centre of the circle which is a direct measure of the depression of the circular locus below the axis. It is closely related to the reactance at the characteristic frequency by the subtraction from the radius of the locus. At the characteristic frequency, the ratio of the current flow through the intra and extra cellular fluids is determined as a function of the ratio of the intra to extra cellular resistance, so that it is independent of the capacitance of the cell membrane. Accordingly, the reactance at the characteristic frequency can be used more accurately as an indicator of extra-cellular fluid levels. Since the reactance at the centre of the circle is directly related to the characteristic reactance, this value is also related to the intra and extra cellular fluid.

Accordingly, the dispersion parameter is not only related to a ratio of extra-cellular to intra-cellular fluid levels, but also takes into account deviation from an idealised equivalent circuit

reflecting the distribution of relaxation times within the subject and so encompasses changes in cell structure. In contrast, if a direct ratio of intra-cellular to extra-cellular fluid is used as an index I this is typically calculated as shown in equation (6) below and therefore does not account for such deviations to the same extent.

$$I = \frac{R_i}{R_e} = \frac{R_\infty}{R_0 - R_\infty} \tag{6}$$

As lymphoedema is characterised by the accumulation of extra-cellular fluid, the dispersion parameter is different between a healthy and oedema affected population, with the difference being more readily quantifiable than if a direct ratio of intra-cellular to extra-cellular, given by equation (6) is used.

An example of the propagation of errors in the calculation of a dispersion parameter alpha and a ratio of intra-cellular to extra-cellular fluid will now be described. In order to determine the propagation of errors, it is necessary to take into account typical measurement errors in different frequency ranges for a typical measurement device, and these are shown in Table 1 below.

Table 1

Frequency Range	**Body Impedance**	**Impedance Error**	**Phase Error**
3 – 100 kHz	200 – 1100 Ohms	+/- 1%	+/- 1%
100 – 1000 kHz	200 – 1100 Ohms	+/- 2%	+/- 2%

In this instance, the relative error in the index I from equation (6) is given by:

$$\frac{\Delta I}{I} = \frac{\Delta R_\infty}{R_\infty} + \frac{\Delta R_0 + \Delta R_\infty}{R_0 + R_\infty}$$

Similarly the relative error in the indicator *Ind* from equation (1) is given by:

$$\frac{\Delta Ind}{Ind} = \frac{\Delta X_C}{X_C} + \frac{\Delta R_0 + \Delta R_\infty}{R_0 - R_\infty}$$

Given the typical errors specifications for the measuring devices outlined in Table 1 above, and taking example leg impedance measurements, this leads to example impedance parameter values of:

$$R_0 = 372\Omega \pm 1\%$$

$$R_\infty = 253\Omega \pm 2\%$$

$$X_C = -28\Omega \pm 1\%$$

Accordingly, this leads to errors of:

$$\frac{\Delta I}{I} = 2 + \frac{0.01 \cdot 372 + 0.02 \cdot 253}{372 + 253} = 2.01\%$$

$$\frac{\Delta Ind}{Ind} = 1 + \frac{0.01 \cdot 372 + 0.02 \cdot 253}{372 - 253} = 1.07\%$$

This demonstrates that the alpha parameter can be determined more accurately and should therefore be more sensitive to fluid level changes within the subject, and hence the presence absence or degree of oedema.

At step 240, the dispersion parameter can be used to determine an indicator. In one example, the indicator provides information relating to the subject, such as an indication of fluid levels within the subject. In one example, the indicator is in the form of a numerical value that depends on a reference, and which can be used to determine the presence, absence or degree of a condition, such as oedema.

In one particular example, the reference is at least partially based on the dispersion parameter of an unaffected body segment. In particular, if the affected body segment does not in fact have oedema, then the dispersion parameter will be similar to the dispersion parameter for the unaffected body segment, thereby minimising a difference between first and second dispersion parameters. In contrast if the affected body segment has oedema the fluid levels

will differ to the fluid levels in the unaffected body segment, meaning that the difference between the first and second dispersion parameters increases. As a result, the magnitude of the difference in first and second dispersion parameters between first and second body segments can be indicative of the presence, absence or degree of oedema. Accordingly, by comparing the difference between the dispersion parameters of affected and unaffected body segments to a threshold amount, then this can therefore be used to determine the presence, absence or degree of oedema.

In one example, the difference is scaled by a scaling factor so that the indicator and the threshold can be a memorable value, such as an integer value, or the like. This can be achieved by calculating an indicator as follows:

$$Ind = sf\left(DP_2 - DP_1\right) \tag{7}$$

where: *Ind* is the indicator

DP_1 is the first dispersion parameter value of the affected body segment

DP_2 is the second dispersion parameter value of the unaffected body segment

sf is a scaling factor

However, a population study of healthy subjects has found inherent differences in fluid levels between different body segments, such as limbs, even in unaffected individuals. This can include slight differences in dispersion parameters due to limb dominance in limbs as well as differences arising if the unaffected and affected limbs are of different limb types, such as arms and legs. For example, the dispersion parameter for a subject's leg will typically differ to that of the subject's arm, even in the absence of oedema in both limbs.

Accordingly, when calculating the reference it is typical to determine a predicted dispersion parameter value for the affected limb based on the second dispersion parameter value determined for the unaffected limb. This is usually achieved using at least one reference value derived from a reference normal population, allowing the natural variations between limbs due to gender, limb dominance and different limb types to be accommodated.

In one particular example, the predicted dispersion parameter value is calculated based on parameters derived by performing a linear regression of first and second dispersion parameter values measured for a reference population. The predicted dispersion parameter value can then be determined using an equation of the form:

$$DP_p = aDP_2 + K \quad (8)$$

where: DP_2 is the second dispersion parameter value

DP_p is the predicted dispersion parameter value

a is a multiplier reference value determined based on a relationship between first and second dispersion parameter values for a reference population

K is a constant reference value determined based on a relationship between first and second dispersion parameter values for the reference population

In one example, for a male subject, the predicted value for a leg segment based on second dispersion parameters for an arm segment is based on a value of a in the range 0.15 to 0.022, and a value of K in the range 0.62 to 0.72. For a female subject, the predicted value for a leg segment based on second dispersion parameters for an arm segment is based on a value of a in the range 0.44 to 0.41, and a value of K in the range 0.43 to 0.46.

When a predicted dispersion parameter value is used, the indicator can be determined using the equation:

$$Ind = \frac{sf \times (DP_p - DP_1)}{3SE} \quad (9)$$

where: Ind is the indicator

DP_1 is a dispersion parameter value determined for the body segment

DP_p is a predicted dispersion parameter value for the body segment

sf is a scaling factor

SE is a standard error determined based on dispersion parameter values in a reference population

It should be noted that in the event that measurements are made for an affected body segment only, then the predicted dispersion parameter value could alternatively be based on a mean value obtained from a reference population, leading to an indicator of the form:

$$Ind = \frac{sf \times \left(DP_{\mu} - DP_1\right)}{3SE} \qquad (10)$$

where: DP_{μ} is the mean dispersion parameter value for a reference normal population

sf is a scaling factor

SE is a standard error determined based on dispersion parameter values for the reference population.

Accordingly, it will be appreciated that the above described dispersion parameter can be used in diagnosing the presence, absence or degree of oedema. Furthermore, in contrast to prior art techniques, a dispersion parameter tends to provide more reliable results, as will be discussed in more detail below.

In the above examples, it will be appreciated that the order of the dispersion parameters could be reversed, so that for example in equation (9) the predicted value could be subtracted from the measured value and this will depend on the nature of the dispersion parameter used, so for example whether the dispersion parameter is based on equations (1), (1A), (1B), (1C), (2), or variations thereof. In general the order used will be selected so that the indicator *Ind* increases in magnitude as the level of oedema increases, however this is not essential and any suitable arrangement may be used.

An example of the process for performing impedance measurements to determine an indicator for limb oedema will now be described in more detail with reference to Figure 4.

In this example, at step 400 subject details are determined and provided to the processing system 102. The subject details will typically include information such as limb dominance, details of any medical interventions, as well as information regarding the subject such as the

subject's age, weight, height, sex, ethnicity or the like. The subject details can be used in selecting a suitable reference normal population, as well as for generating reports, as will be described in more detail below.

It will be appreciated that the subject details may be supplied to the processing system 102 via appropriate input means, such as the I/O device 105. Thus, each time a subject measurement is performed this information can be input into the measuring device 100.

However, more typically the information is input a single time and stored in an appropriate database, or the like, which may be connected as a peripheral device 104 via the external interface 103. The database can include subject data representing the subject details, together with information regarding previous oedema indicators, baseline measurements or impedance measurements recorded for the subject.

In this instance, when the operator is required to provide subject details, the operator can use the processing system 102 to select a search database option allowing the subject details to be retrieved. This is typically performed on the basis of a subject identifier, such as a unique number assigned to the individual upon admission to a medical institution, or may alternatively be performed on the basis of name or the like. Such a database is generally in the form of an HL7 compliant remote database, although any suitable database may be used.

In one example, the subject can be provided with a wristband or other device, which includes coded data indicative of the subject identifier. In this case, the measuring device 100 can be coupled to a peripheral device 104, such as a barcode or RFID (Radio Frequency Identification) reader allowing the subject identifier to be detected and provided to the processing system 102, which in turn allows the subject details to be retrieved from the database. The processing system 102 can then display an indication of the subject details retrieved from the database, allowing the operator to review these and confirm their accuracy before proceeding further.

At step 410 the affected limb, or "at risk" limb, is determined. This may be achieved in any one of a number of ways depending on the preferred implementation. Thus, for example, the affected limb can be indicated through the use of appropriate input means, such as the I/O

device 105. Alternatively this information can be derived directly from the subject details, which may include an indication of the affected limb, or details of any medical interventions performed, which are in turn indicative of the affected limb.

At step 420 an operator positions the electrodes on the subject S, and connects the leads 123, 124, 125, 126, to allow the impedance measurements to be performed. The general arrangement is to provide electrodes on the hand at the base of the knuckles and between the bony protuberances of the wrist, as shown in Figure 5A, and on the feet at the base of the toes and at the front of the ankle, as shown in Figure 5B. The configurations shown in Figures 5C and 5D allow the right arm 531 and the right leg 533 to be measured respectively, and it will be appreciated that equivalent arrangements can be used to measure the impedance of the left leg and left arm.

It will be appreciated that this configuration uses the theory of equal potentials, allowing the electrode positions to provide reproducible results for impedance measurements. For example when current is injected between electrodes 113A and 113B in Figure 5C, the electrode 115B could be placed anywhere along the left arm 532, since the whole arm is at an equal potential.

This is advantageous as it greatly reduces the variations in measurements caused by poor placement of the electrodes by the operator. It also greatly reduces the number of electrodes required to perform segmental body measurements, as well as allowing the limited connections shown to be used to measure each limb separately.

However, it will be appreciated that any suitable electrode and lead arrangement may be used.

At step 430 the impedance of the affected and unaffected limbs are measured. This is achieved by applying one or more current signals to the subject and then measuring the corresponding voltages induced across the subject S. It will be appreciated that in practice the signal generators 117A, 117B, and the sensors 118A, 118B, return signals to the processing system 102 indicative of the applied current and the measured voltage, allowing impedances to be determined.

Following at step 440 a dispersion parameter *DP* for each of the limbs is determined using equations (1) or (2) above.

At step 450 a reference is selected. The reference is typically derived from equivalent measurements made on a normal population (subject's not suffering from oedema) that is relevant to the subject under study. Thus, the normal population is typically selected taking into account factors such as medical interventions performed, ethnicity, sex, height, weight, limb dominance, the affected limb, or the like.

Therefore if the test subject is female having bilateral lymphoedema of the dominant leg then the normalised data drawn from the normal population database will be calculated from the dominant leg impedance ratio measurements from female subjects that are present in the normal population database.

Accordingly, at this stage the processing system 102 typically accesses reference populations stored in the database, or the like. This may be performed automatically by the processing system 102 using the subject details. Thus for example, the database may include a look-up table that specifies the normal population that should be used given a particular set of subject details. Alternatively selection may be achieved in accordance with predetermined rules that can be derived using heuristic algorithms based on selections made by medically qualified operators during previous procedures. Alternatively, this may be achieved under control of the operator, depending on the preferred implementation.

It will be appreciated by persons skilled in the art that operators may have their own reference stored locally. However, in the event that suitable references are not available, the processing system 102 can be used to retrieve a reference from a central repository, for example via an appropriate server arrangement. In one example, this may be performed on a pay per use basis.

Alternatively, in the event that a suitable reference is not available predetermined standard reference values may be used, as described above. However it will be appreciated that different values can be used as appropriate and that these values are for illustration only.

At step 460 a predicted dispersion parameter value for the affected body segment is determined using the second dispersion value derived for the unaffected body segment and the reference values, as described above with respect to equation (8).

Following this an indicator can be determined using equation (9) at step 470. As described above, this is typically achieved by scaling the difference between the predicted and measured dispersion parameter values for the affected arm. This is performed so that the value of the indicator at a threshold indicative of the presence of oedema corresponds to a memorable value. In one example, the scaling factor is set so that an indicator value of greater than "10" is indicative of oedema, whilst a value of below "10" is used to indicate an absence of oedema.

Representations of the indicator can then optionally be displayed at step 480. Examples of such representations for oedema indicators will now be described with reference to Figures 6A and 6B.

In these examples, the representation is in the form of a linear indicator 600, having an associated scale 601 and a pointer 602. The position of the pointer 602 relative to the scale 601 is indicative of the subject parameter, which in this example is based on an impedance ratio representing a ratio of fluid levels determined for healthy and affected limbs of the subject.

In the example of Figure 6A, the indicator representation also includes a mean indicator 610 representing the mean indicator for the normal population, which is set to a value of "0" on the scale 601. The upper and lower thresholds are set to be three standard deviations from the mean 610, and are set to be positioned at "-10" and "+10" on the scale 601 respectively.

In use the lower and upper thresholds 611, 612 define a normal range 620, an investigation range 621, and an oedema range 622. The ranges can be indicated through the use of background colours on the linear indicator, so that for example, the normal range 620 is shaded green, whilst the investigation range 621 is unshaded, and the oedema range 622 is shaded red. This allows an operator to rapidly evaluate the positioning of the pointer 602

within the ranges, allowing for fast and accurate diagnosis of oedema based on the indicated fluid level information.

Thus, in the example of Figure 6A, the pointer 602 is positioned at the value of 16.6, placing the pointer 602 in the oedema range 622, indicating to the user that the fluid levels in the subject S are probably indicative of oedema in the affected limb.

In this example, the linear indicator extends up to a value of "20" as this is able to accommodate the determined value of 16.6. However, it will be appreciated that the linear indicator can be extended to any value required to accommodate the determined indicator value. To ensure that the linear scale remains clear, particularly if an extreme indicator value is to be displayed, the linear indicator 600 may include discontinuities, allowing the scale to be extended to higher values. An example of this is shown in Figure 6C, in which a discontinuity 605 is used to separate the linear indicator 600 into two portions 600A, 600B. In this example, the linear indicator portion 600A extends from "-10" to "+20", whilst the second linear indicator portion 600B extends from "+70" to "+90", thereby allowing an indicator value of "80" is to be displayed by appropriate positioning of the pointer 602 in the indicator portion 605B.

Whilst a linear indicator 600 is preferred as this easily demonstrates to the operator the potential degree of severity of any oedema, this is not essential, and alternatively the scale may be modified, particularly if an outlier indicator value is determined. Thus, for example, the linear indicator could include logarithmic scaling, or the like, over all or part of its length, to allow the determined indicator value to be displayed.

In the event that the indicator value is between "-10" and "+10", this indicates that the subject S is within the normal range 620 and that therefore they do not have oedema. Finally, in the event that the indicator value is below "-10", then the subject S is within the investigation range 621, indicating that the measurements need to be investigated further. In particular, it is extremely unlikely that the affected limb could have an impedance value significantly smaller than that of the unaffected limb, and accordingly, this indicates that in all likelihood there has been an error in the measurement, such as incorrect designation of the affected limb, or incorrect connection of electrodes.

In the example of Figure 6B, no reference is available, and accordingly, the representation does not includes a mean 610 or lower or upper thresholds 611, 612. In this instance, the indicator value is still scaled using default standard values. This may be used if the indicator is determined based on equation (7).

As a result an oedema indicator value of above "10" is still indicative of oedema, but may be a less reliable indicator than if the reference is available. To take this into account, the thresholds 611, 612, and hence the specific ranges 620, 621, 622, are excluded from the representation, highlighting to the operator that the scaled subject parameter value is indicative but not definitive of the subject's oedema status.

Experimental Examples

A survey of the normal population was conducted using an Impedimed SFB7 device to determine the "normal" values for the Cole parameters. 65 self diagnosed healthy females and 29 self diagnosed healthy males participated in a trial with the population demographics being shown in Table 2. The average and standard deviation of the Cole parameters for each limb was determined for both the dominant and non dominant limbs.

Table 2

	Male	Female
Age (years) μ(σ)	40.1 (13.2)	42.6 (11.7)
Height (cm) μ(σ)	179.6 (7.5)	162.6 (21.3)
Weight (kg) μ(σ)	86.6 (16.9)	69.4 (16.9)

Of the single Cole parameters, α is the parameter that has the lowest variation for all limbs within a normal population (COV = 1-3%), thereby indicating that this is generally a more consistent parameter for healthy individuals.

The variation of some combinations of the Cole parameters was also investigated. The parameters with the lowest coefficient of variation in a control population were R_0/R_∞, R_0/X_c. R_i/R_e has a large coefficient of variation (10-15%) which suggests that this would make it difficult to use this impedance ratio to successfully distinguish between inherent variations within a subject, and variations induced by the presence of oedema or lymphoedema.

The normal arm to leg ratio calculated from the reference data for the same Cole parameters again results in the parameters having the lowest variation (<5%) being α, R_0/R_∞ and R_0/X_c.

To evaluate a bilateral approach, leg data from leg lymphoedema sufferers was obtained. Data was collected during a clinical trial in which 30 volunteers were invited to participate. Each subject was classified into the Control, Bilateral Lymphoedema or Unilateral Lymphoedema group based on provided medical history. Subjects were required to lie in a supine position while electrodes were attached to the hands and feet using standard placement markers. Three swept frequency bioimpedance measurements of each limb were recorded.

The population demographics are shown in Table 3 for the subjects who met eligibility criteria. The mean subject age was significantly higher than for the normal data previously collected in a healthy population. The mean heights for both trials are comparable and the mean weight for the control subjects was comparable to the normal data collected previously. However the unilateral and bilateral subjects recorded higher weights. This is to be expected as the amount of fluid in a leg affected by lymphoedema will contribute to the weight.

Table 3

	Control (M/F)	Unilateral (M/F)	Bilateral (M/F)
Gender	4/6	3/8	4/4
Age (years) μ(σ)	59.3 (4.0) / 48.5 (21.6)	61.4 (12.5) / 59.1 (13.1)	63.0 (14.6) / 65.8 (11.8)
Height (cm) μ(σ)	179.8 (2.4) / 165.5 (6.7)	180.7 (4.0) / 161.9 (10)	177.5 (6.9) / 163.5 (5.3)
Weight (kg) μ(σ)	84.8 (3.8) / 65.8 (11.1)	89.3 (10.2) / 75.4 (15.2)	123.0 (31.1) / 93.5 (24.8)

A review of the COV in Table 2 suggests that other parameters other than R_i/R_e are more stable within a normal population. These are the R_0/R_∞, Ro/ X_c and α parameters.

An indicator was derived for each single limb from the R_0/R_∞, Ro/ X_c and α parameters. The results for an indicator calculated based on α are shown in table 46, using a reference from a standard population. The indicator is calculated for each limb independently using a reference value for α obtain from the reference normal population, as shown in equation (10).

Table 4

Subject No	Gender	Group	Ind	Ind Non	Ind Dom	Ind Non

			Dom Arm	Dom Arm	Leg	Dom Leg
UB500-01-01	Female	Control	0.8	-0.1	-2.0	-1.3
UB500-01-09	Female	Control	-2.3	-3.0	-6.2	-5.4
UB500-01-13	Female	Control	-3.5	-0.6	-6.4	-6.5
UB500-01-14	Female	Control	-7.8	-5.8	-7.5	-9.1
UB500-01-24	Female	Control	-5.7	-2.3	-9.6	-7.4
UB500-01-25	Female	Control	2.3	3.3	-5.5	-1.7
UB500-01-02	Male	Control	-1.2	-0.1	-3.8	-4.2
UB500-01-17	Male	Control	-6.7	**-11.5**	-8.7	**-11.0**
UB500-01-23	Male	Control	-6.0	-2.8	-9.0	-5.2
UB500-01-29	Male	Control	1.7	6.5	-7.3	-2.6
UB500-01-04	Female	Uni	-3.4	-1.0	-7.6	**-15.2**
UB500-01-05	Female	Uni	-2.7	-6.3	-7.6	**-15.0**
UB500-01-12	Female	Uni	-3.9	-3.4	**-14.4**	-7.4
UB500-01-15	Female	Uni	0.4	0.1	**-10.4**	**-29.8**
UB500-01-22	Female	Uni	-9.0	-4.9	**-16.8**	**-13.8**
UB500-01-26	Female	Uni	-0.4	-1.4	**-16.3**	**-11.9**
UB500-01-28	Female	Uni	-2.1	1.7	**-10.0**	-4.9
UB500-01-08	Male	Uni	0.3	4.9	**-15.0**	-0.4
UB500-01-18	Male	Uni	-0.2	1.3	**-16.9**	**-10.2**
UB500-01-03	Female	Bi	-3.3	-1.2	**-8.6**	**-8.6**
UB500-01-07	Female	Bi	-3.2	-1.8	**-23.6**	**-27.3**
UB500-01-11	Female	Bi	**-11.1**	**-12.3**	**-19.7**	**-21.2**
UB500-01-19	Female	Bi	-5.2	-6.5	**-34.9**	**-26.3**
UB500-01-06	Male	Bi	0.6	5.5	**-27.6**	**-32.2**
UB500-01-10	Male	Bi	**-20.0**	**-28.4**	**-27.5**	**-24.1**
UB500-01-20	Male	Bi	-7.4	**-22.7**	**-26.2**	**-19.9**
UB500-01-27	Male	Bi	-1.7	2.6	**-22.8**	**-20.0**

In this example, the indicator values are negative as the reference dispersion parameter was subtracted from the measured value (the reverse situation to that shown in equation (10)) and as α decreases with an increase in lymphoedema. In this example, the scaling factor is selected so that -10 is an indication of lymphoedema.

Table 5 shows the specificity and sensitivity of the dispersion parameter α in being indicative of the presence of lymphodema. These results are greatly improved compared to using an R_i/R_e ratio for each limb. It should be noted that the sensitivity of the arms cannot be calculated as no affected arms were measured.

Table 5

	Dom Arm	Non Dom Arm	Dom Leg	Non Dom Leg
Specificity (%)	93	85	80	86
Sensitivity (%)	n/a	n/a	92	92

The biggest concern for this approach is the high indicator value recorded for three of the arms of the subjects. It would be expected that the indicator calculated for these unaffected arms would be within the normal range. In addition, the positive assessment of lymphoedema in some of the unaffected legs of the unilateral subjects may not be a false positive, but rather a sign that the lymphoedema is present in both legs.

The results highlight the ability to assess the presence of lymphoedema from the measurement of a single affected limb, meaning that this allows a technique to be implemented that requires only a single measurement of the affected limb.

Arm to leg ratios that resulted in a low coefficient of variation were again R_0/R_∞, R_0/X_c and α. From these, an indicator was calculated for the dominant and non dominant leg from the arm to leg ratios, similar to equation (7). The parameter that showed the greatest effectiveness is the ratio of arm to leg for the dispersion parameter α. Table 6 shows the specificity and sensitivity using this method is still low.

Table 6

	Dom Leg	Non Dom Leg
Specificity (%)	87	93
Sensitivity (%)	42	54

The above results suggest that perhaps the relationship between the arm and leg is not a one to one relationship. The ratio of affected to unaffected limb approach works well with unilateral lymphoedema as the affected limb is compared to an equivalent but contra-lateral limb. The ratio of unaffected limb to affected limb is very close to 1. This is the equivalent of assuming a linear relationship between the limbs without a constant offset. That is $y = mx + c$ without the intercept c and where m is the normal ratio.

In essence this uses the healthy limb to predict what we would expect the affected limb to be if it were also unaffected. The deviation of the expected result from the measured result is then compared to the normal variation within a healthy population to assess the presence of lymphoedema. In the case of comparing an arm to a leg, there are a number or differences in geometry and structure such as cross sectional area and length. This would indicate an

additional offset between the two measurements and suggest that the relationship between arms and legs may be linear. These concepts are shown graphically in Figure 7.

An example of the variation of a normal leg α with normal arm α is shown for dominant arms and legs for healthy females in Figure 8. This data is collected using the ImpediMed SFB7. No outliers have been rejected in this instance.

Regression analysis was performed on the healthy male and female, dominant and non dominant limb data to determine the line of best fit for the chosen parameters. The female normal data shows a stronger association (R > 0.5) than the male data (R = 0.2) for all parameters.

The resulting linear equations used to predict leg data from arm data are grouped by gender and dominance. The best performing parameter is α. The equations are shown below.

- Female Dominant: $\alpha_{leg} = 0.4416\alpha_{arm} + 0.4379$, SE = 0.0136
- Female Non Dominant: $\alpha_{leg} = 0.4176\alpha_{arm} + 0.4581$, SE = 0.0136
- Male Dominant: $\alpha_{leg} = 0.1572\alpha_{arm} + 0.6227$, SE = 0.0113
- Male Non Dominant: $\alpha_{leg} = 0.0217\alpha_{arm} + 0.7145$, SE = 0.0109

These regression equations were then used to predict the expected leg α from the measured arm α, using equation (8) above. Next the predicted leg α was subtracted from the measured leg α. This difference between the actual and predicted result was then compared to the standard error for a normal population. An indicator value was calculated according to equation (9).

Example results for leg α predicted from arm measurements are shown in Table 7.

Table 7

Subject No	Gender	Group	indicator Dom Leg	Indicator Non Dom Leg
UB500-01-01	Female	Control	2.8	1.5
UB500-01-09	Female	Control	7.4	6.4
UB500-01-13	Female	Control	5.2	7.3

UB500-01-14	Female	Control	3.9	6.8
UB500-01-24	Female	Control	7.6	7.3
UB500-01-25	Female	Control	2.4	5.4
UB500-01-02	Male	Control	6.5	3.9
UB500-01-17	Male	Control	6.8	7.5
UB500-01-23	Male	Control	6.9	6.0
UB500-01-29	Male	Control	9.4	3.0
UB500-01-04	Female	Uni	6.7	**17.4**
UB500-01-05	Female	Uni	7.2	**13.5**
UB500-01-12	Female	Uni	**19.7**	8.5
UB500-01-15	Female	Uni	**12.3**	**35.3**
UB500-01-22	Female	Uni	**14.1**	**13.0**
UB500-01-26	Female	Uni	**16.7**	**21.2**
UB500-01-28	Female	Uni	**16.0**	**28.5**
UB500-01-08	Male	Uni	**10.3**	7.1
UB500-01-18	Male	Uni	**14.5**	4.5
UB500-01-03	Female	Bi	8.0	9.5
UB500-01-07	Female	Bi	**32.8**	**37.6**
UB500-01-11	Female	Bi	**16.2**	**16.8**
UB500-01-19	Female	Bi	**48.7**	**36.0**
UB500-01-06	Male	Bi	**24.9**	**30.5**
UB500-01-10	Male	Bi	**15.4**	**13.5**
UB500-01-20	Male	Bi	**27.5**	**20.3**
UB500-01-27	Male	Bi	**24.4**	**20.6**

These results highlight that the use of the dispersion parameter α together with the prediction of an expected value for the affected limb based on measurements for the unaffected limb provide a high reliability of identification of lymphoedema as highlighted by sensitivity and specificity measures shown in Table 8. Of all methods presented, the results demonstrate the highest specificity and sensitivity.

Table 8

	Dom Leg	Non Dom Leg
Specificity (%)	80	93
Sensitivity (%)	92	92

It should be noted that Bilateral subject UB500-01-03 did not record an indicator of greater than 10. This can be explained as the subject had a very mild case of lymphoedema affecting only the upper most part of the thigh. It is expected that the contribution of the lymphoedema to the measured bioimpedance was not significant to be greatly altered from the normal state. However it will be noticed that in both legs an indicator score was obtained that was greater than 8.

The remaining unilateral subjects whose unaffected leg produced an indicator of greater than 10, are potentially showing signs of developing lymphoedema in the other leg.

Accordingly, this highlights that using a dispersion parameter has been shown to produce the best results in predicting the presence of lymphoedema.

Persons skilled in the art will appreciate that numerous variations and modifications will become apparent. All such variations and modifications which become apparent to persons skilled in the art, should be considered to fall within the spirit and scope that the invention broadly appearing before described.

Thus, for example, it will be appreciated that features from different examples above may be used interchangeably where appropriate. Furthermore, whilst the above examples have focussed on a subject such as a human, it will be appreciated that the measuring device and techniques described above can be used with any animal, including but not limited to, primates, livestock, performance animals, such race horses, or the like.

The above described processes can be used for determining the health status of an individual, including the body composition of the individual, or diagnosing the presence, absence or degree of a range of conditions and illnesses, including, but not limited to oedema, lymphoedema, or the like. It will be appreciated from this that whilst the above examples use the term oedema indicator, this is for the purpose of example only and is not intended to be limiting. Accordingly, the oedema indicator can be referred to more generally as an indicator when used in analysing impedance measurements with respect to more general health status information such as body composition, or the like.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1) A method for use in analysing impedance measurements performed on a subject, the method including, in a processing system:
   a) determining at least one impedance value at each of a number of frequencies, each impedance value representing the impedance of a segment of the subject;
   b) determining a dispersion parameter value indicative of a dispersion of the impedance values; and,
   c) determining an indicator based at least in part on the dispersion parameter value.

2) A method according to claim 1, wherein the method includes, in the processing system:
   a) determining first and second dispersion parameter values for first and second body segments respectively; and,
   b) determining the indicator using the first and second dispersion parameter values.

3) A method according to claim 2, wherein the first body segment is an affected body segment and the second body segment is an unaffected body segment.

4) A method according to claim 2 or claim 3, wherein at least one of the body segments is a dominant limb and the other body segment is a non-dominant limb.

5) A method according to any one of the claims 2 to 4, wherein the first body segment is a different body segment to the second body segment.

6) A method according to any one of the claims 2 to 5, wherein the method includes, in the processing system:
   a) determining a predicted dispersion parameter value for the first body segment using the second dispersion parameter value;
   b) determining the indicator using the first and predicted dispersion parameter values.

7) A method according to claim 6, wherein predicted dispersion parameter value is determined to take into account at least one of:
   a) limb dominance; and,
   b) differences in limb types.

8) A method according to claim 6 or claim 7, wherein the method includes, in the processing system, determining a predicted dispersion parameter value using at least one reference value derived from a reference normal population.

9) A method according to claim 8, wherein the reference normal population is selected based on at least one of:

a) limb dominance;

b) differences in limb types;

c) ethnicity;

d) age;

e) gender;

f) weight; and,

g) height.

10) A method according to claim 8 or claim 9, wherein the at least one reference value is determined based on a linear regression of first and second dispersion parameter values measured for the reference normal population.

11) A method according to any one of the claims 6 to 10, wherein the method includes, in the processing system, determining the predicted dispersion parameter value using an equation of the form:

$$DP_p = aDP_2 + K$$

where: DP_2 is the second dispersion parameter value

DP_p is the predicted dispersion parameter value

a is a multiplier reference value determined based on a relationship between first and second dispersion parameter values in a reference population

K is a constant reference value determined based on a relationship between first and second dispersion parameter values in a reference population

12) A method according to claim 11, wherein, for a male subject, the predicted value for a leg segment based on second dispersion parameters for an arm segment is based on:

a) a value of a in the range 0.15 to 0.022; and,

b) a value of K in the range 0.62 to 0.72.

13) A method according to claim 11, wherein, for a female subject, the predicted value for a leg segment based on second dispersion parameters for an arm segment is based on:

a) a value of a in the range 0.44 to 0.41; and,

b) a value of K in the range 0.43 to 0.46.

14) A method according to any one of the claims 6 to 13, wherein the method includes, in the processing system, determining the indicator using the equation:

$$Ind = \frac{sf \times (DP_p - DP_1)}{3SE}$$

where: *Ind* is the indicator

DP_1 is a dispersion parameter value determined for the body segment

DP_p is a predicted dispersion parameter value for the body segment

sf is a scaling factor

SE is a standard error determined based on dispersion parameter values in a reference population

15) A method according to any one of the claims 6 to 13, wherein the method includes, in the processing system, determining the indicator using the equation:

$$Ind = \frac{sf \times (DP_\mu - DP_1)}{3SE}$$

where: DP_μ is the mean dispersion parameter value for a reference normal population

DP_1 is a dispersion parameter value determined for the body segment

sf is a scaling factor

SE is a standard error determined for the dispersion parameter values for the reference population

16) A method according to claim 14 or claim 15, wherein the scaling factor is selected so that a threshold value indicative of the presence or absence of oedema is an integer value.

17) A method according any one of the claims 1 to 16, wherein the method includes, in the processing system, determining the indicator based on the equation:

$$Ind = sf(DP_2 - DP_1)$$

where: *Ind* is the indicator

DP_1 is a first dispersion parameter value for a first body segment

DP_2 is a second dispersion parameter value for a second body segment

sf is a scaling factor

18) A method according to any one of the claims 1 to 17, wherein the dispersion parameter value is indicative of the distribution of impedance measurements for the respective body segment.

19) A method according to any one of the claims 1 to 18, wherein the dispersion parameter is based on the value of at least one of:

$$DP = \frac{(R_0 - R_\infty)}{X_c}$$

$$DP = \frac{X_c}{(R_0 - R_\infty)}$$

$$DP = \frac{(R_\infty - R_0)}{X_c}$$

$$DP = \frac{X_c}{(R_\infty - R_0)}$$

where: R_∞ = impedance at infinite applied frequency;

R_0 = impedance at zero applied frequency;

X_c = reactance at the centre of the circle.

20) A method according to any one of the claims 1 to 19, wherein the dispersion parameter is based on the value of:

$$\alpha = \frac{2}{\pi} a\tan\frac{(R_0 - R_\infty)}{2|X_c|}$$

21) A method according to any one of the claims 1 to 20, wherein the indicator is at least one of:

a) an oedema indicator for use in assessing a presence, absence or degree of oedema in the subject.

b) a hydration indicator for use in assessing hydration levels in a subject.

22) A method according to any one of the claims 1 to 21, wherein the method includes, in the processing system, displaying a representation of the indicator.

23) A method according to claim 22, wherein representation of the indicator includes a linear scale including:

a) a linear indicator;

b) a scale; and,

c) a pointer, the pointer being positioned on the scale in accordance with the indicator.

24) A method according to claim 23, wherein the method includes, in the processing system, displaying a representation including an indication of a change in indicator value from at least one of a previous indicator value and a baseline indicator value.

25) A method according to any one of the claims 21 to 24, wherein the method includes, in the processing system:

a) determining at least one threshold using a reference; and,

b) displaying the threshold as part of the representation.

26) A method according to claim 25, wherein the method includes, in the processing system:

a) determining two thresholds using a reference; and,

b) displaying the thresholds on the representation, the thresholds being indicative of a normal range.

27) A method according to any one of the claims 21 to 26, wherein the method includes, in the processing system, displaying, on the representation, at least one of:

a) a normal range;

b) an intervention range;

c) a hydration range; and,

d) an oedema range.

28) A method according to any one of the claims 1 to 27, wherein the method includes in the processing system, causing one or more impedance measurements to be performed.

29) A method according to any one of the claims 1 to 28, wherein the method includes, in the processing system:

a) causing at least one excitation signal to be applied to the subject;

b) determining at least one signal measured across the subject; and,

c) determining at least one impedance value using an indication of the excitation signal and the signal measured across the subject.

30) A method according to any one of the claims 1 to 29, wherein the method includes, in the processing system:

a) controlling a signal generator to thereby cause the at least one excitation signals to be applied to the subject; and,

b) determining the at least one signal measured across the subject using a sensor.

31) Apparatus for use in analysing impedance measurements performed on a subject, the apparatus including a processing system for:

a) determining at least one impedance value at each of a number of frequencies, each impedance value representing the impedance of a segment of the subject;

b) determining a dispersion parameter value indicative of a dispersion of the impedance values; and,

c) determining an indicator based at least in part on the dispersion parameter value.

32) Apparatus according to claim 31, wherein the apparatus includes:

a) a signal generator for applying one or more electrical signals to the subject using a first set of electrodes;

b) a sensor for measuring electrical signals across a second set of electrodes applied to the subject; and,

c) a controller for:

i) controlling the signal generator; and,

ii) determining the indication of the measured electrical signals.

33) Apparatus according to claim 31, wherein the controller includes the processing system.

34) Apparatus according to claim 31, wherein the processing system includes the controller.

35) Apparatus according to any one of the claims 30 to 33, wherein the apparatus is for performing the method of any one of the claims 1 to 29.

36) A method for use diagnosing the presence, absence or degree of oedema in a subject by using impedance measurements performed on the subject, the method including, in a processing system:

a) determining at least one impedance value at each of a number of frequencies, each impedance value representing the impedance of a segment of the subject;

b) determining a dispersion parameter value indicative of a dispersion of the impedance values;

c) determining an indicator based at least in part on the dispersion parameter value; and,

d) displaying a representation of the indicator, to thereby allow the presence, absence or degree of oedema in the subject to be assessed.

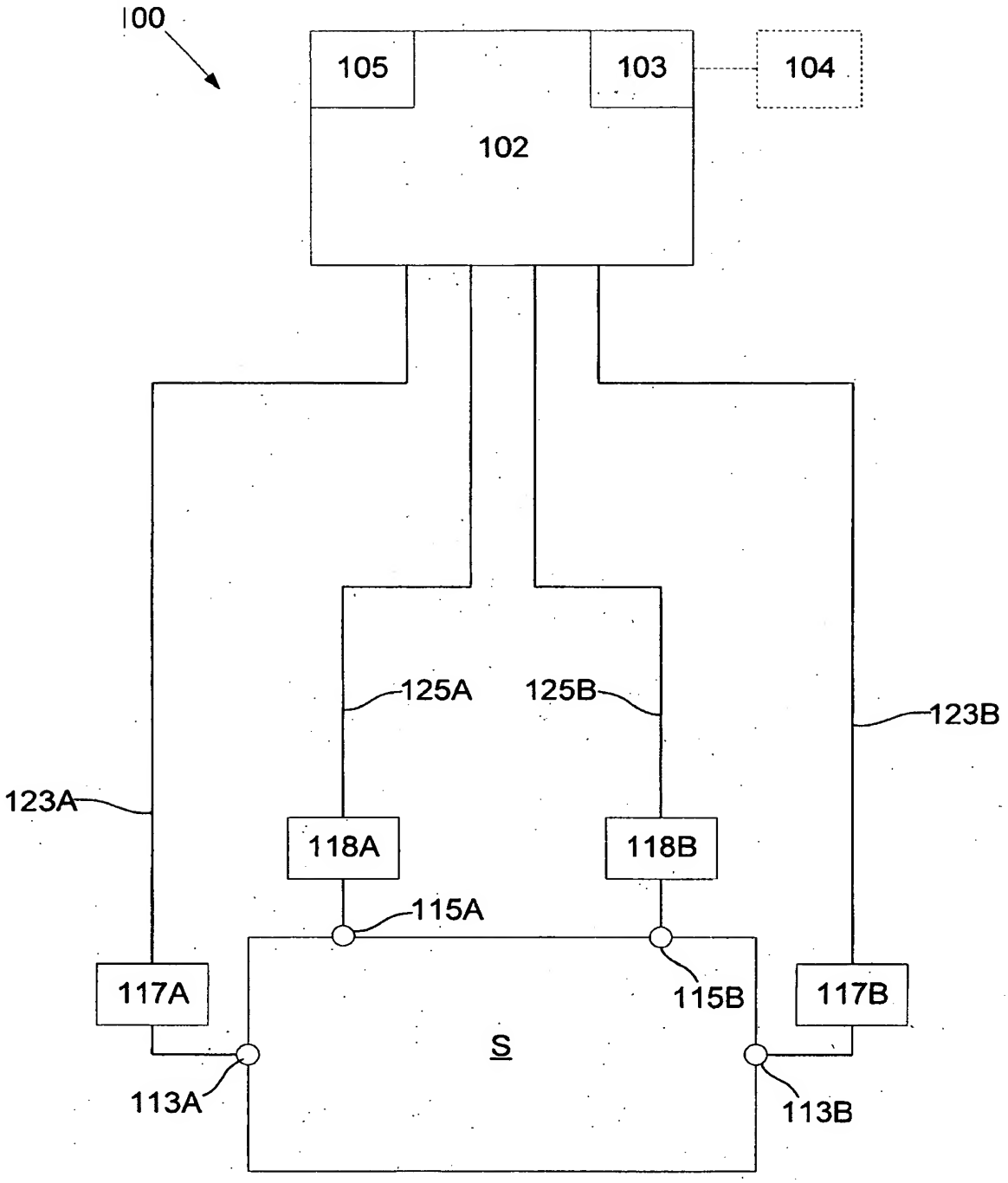
100
105
103
104
102
125A
125B
123B
123A
118A
118B
115A
117A
115B
117B
S
113A
113B

Fig. 1

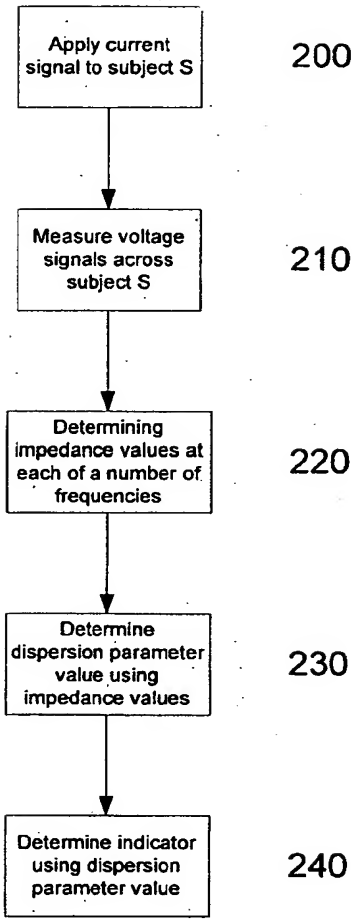
Apply current signal to subject S
200
Measure voltage signals across subject S
210
Determining impedance values at each of a number of frequencies
220
Determine dispersion parameter value using impedance values
230
Determine indicator using dispersion parameter value
240

Fig. 2

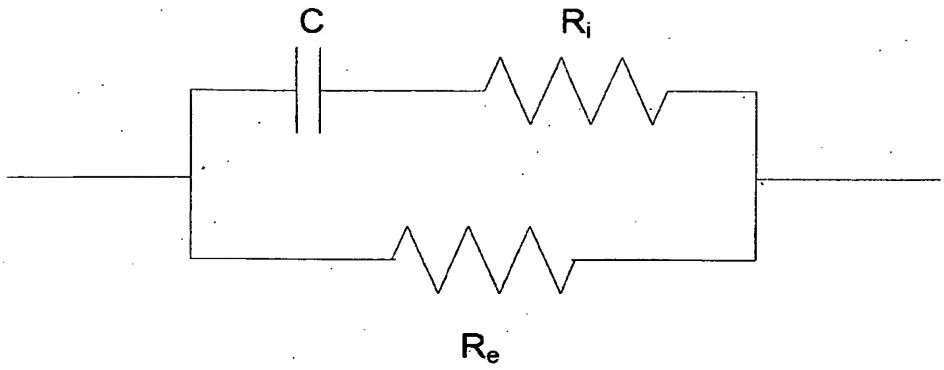
C
R_i
R_e

Fig. 3A

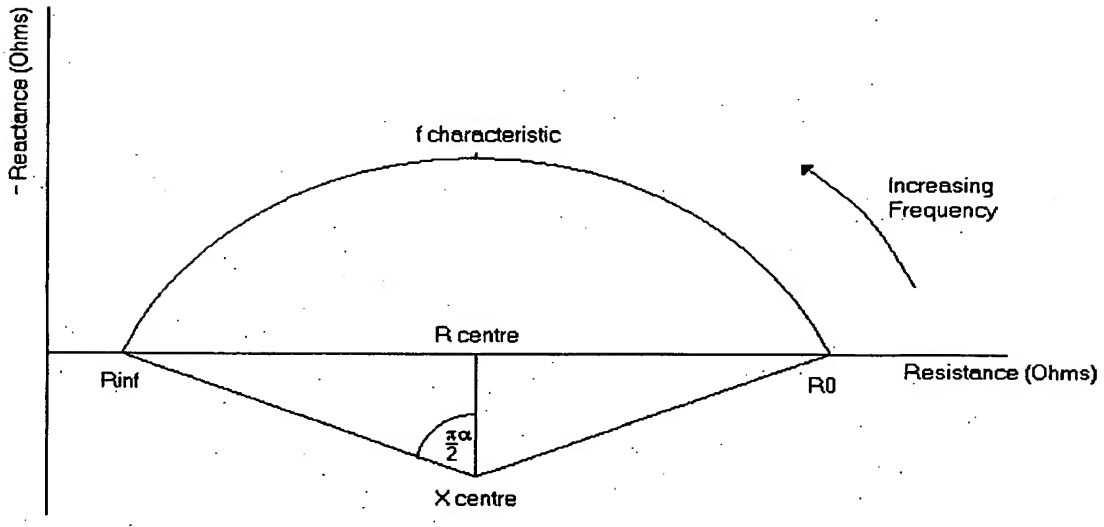
- Reactance (Ohms)
f characteristic
Increasing Frequency
R centre
Rinf
R0
Resistance (Ohms)
$\frac{\pi\alpha}{2}$
X centre

Fig. 3B

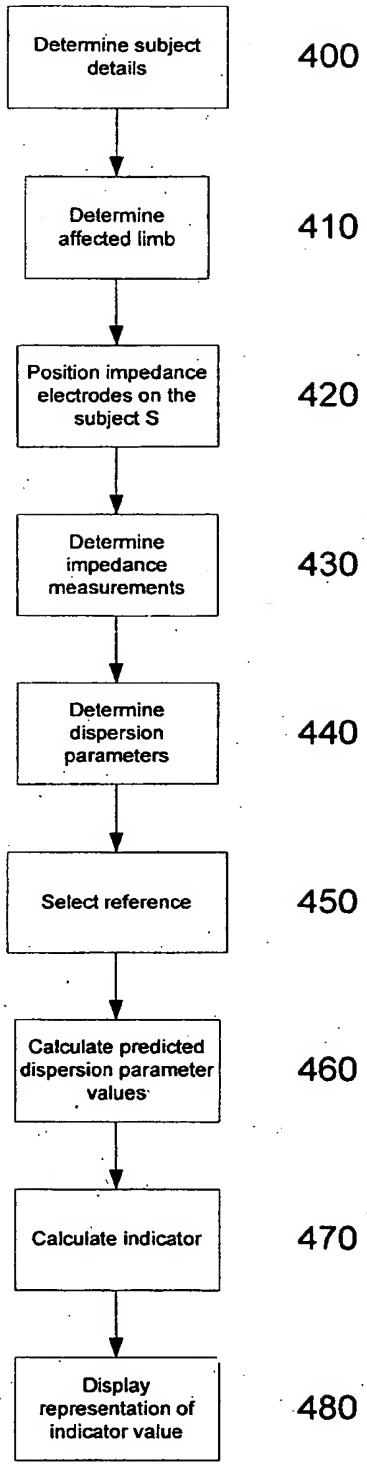
Determine subject details
400
Determine affected limb
410
Position impedance electrodes on the subject S
420
Determine impedance measurements
430
Determine dispersion parameters
440
Select reference
450
Calculate predicted dispersion parameter values
460
Calculate indicator
470
Display representation of indicator value
480

Fig. 4

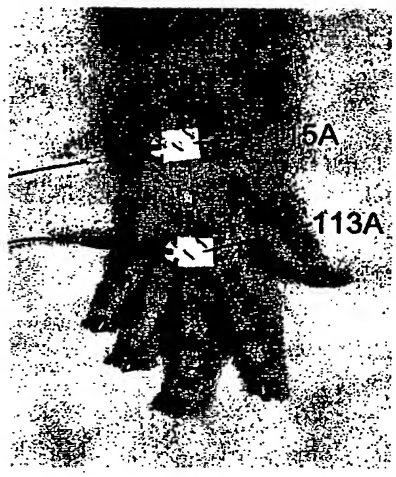

Fig. 5A

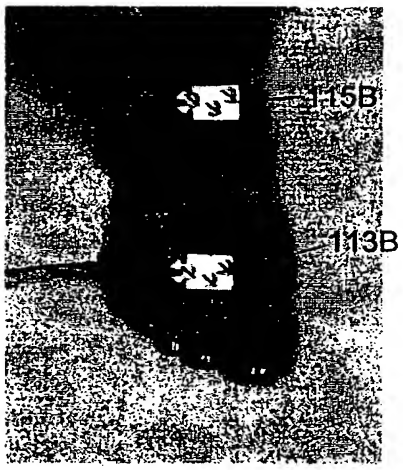

Fig. 5B

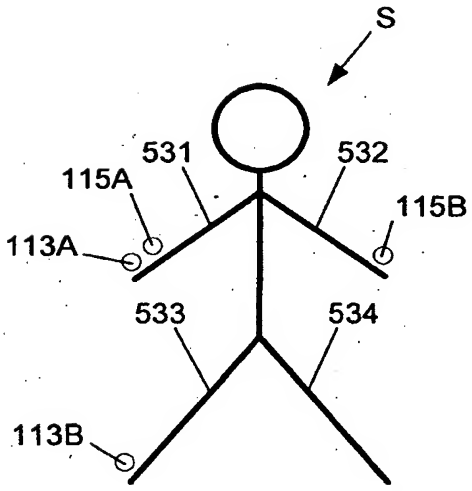

Fig. 5C

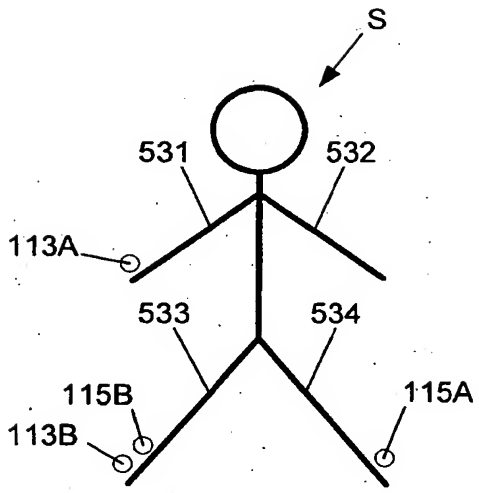

Fig. 5D

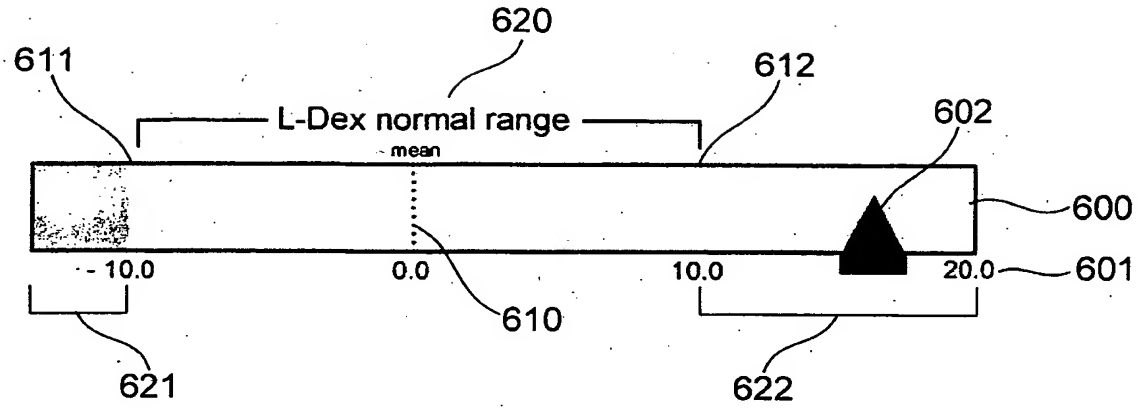

Fig. 6A

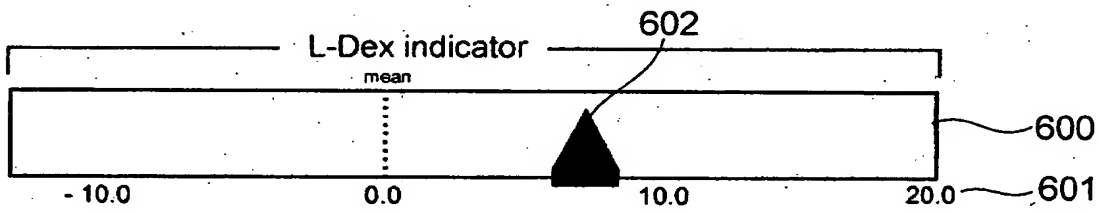

Fig. 6B

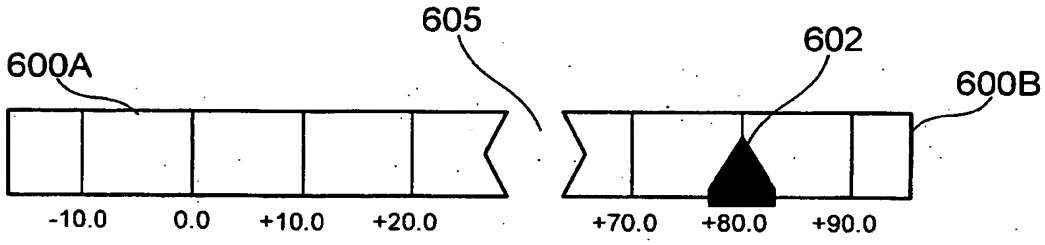

Fig. 6C

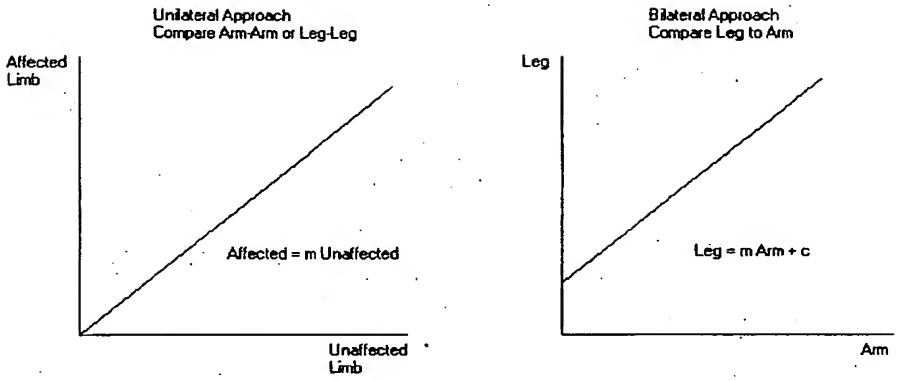
Unilateral Approach
Compare Arm-Arm or Leg-Leg
Affected Limb
Affected = m Unaffected
Unaffected Limb
Bilateral Approach
Compare Leg to Arm
Leg
Leg = m Arm + c
Arm

Fig. 7

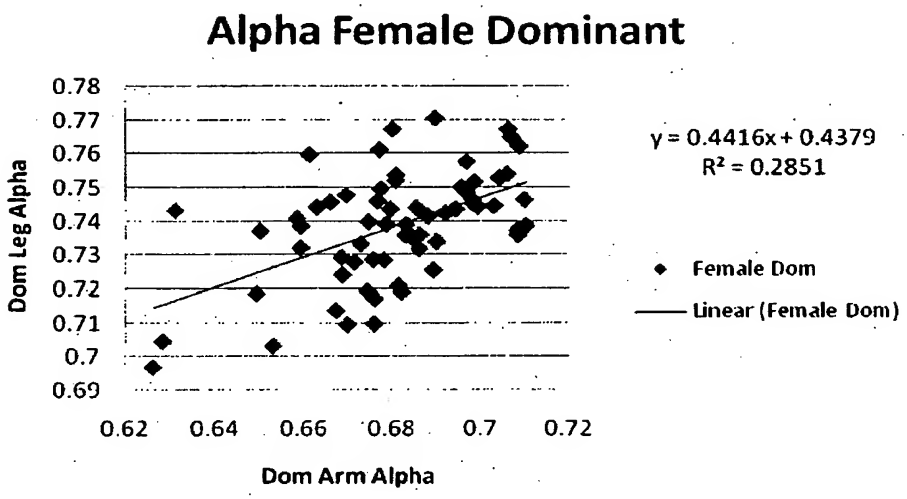
Alpha Female Dominant
Dom Leg Alpha
0.78
0.77
0.76
0.75
0.74
0.73
0.72
0.71
0.7
0.69
0.62
0.64
0.66
0.68
0.7
0.72
Dom Arm Alpha
y = 0.4416x + 0.4379
R² = 0.2851
Female Dom
Linear (Female Dom)

Fig. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2010/001399

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

A61B 5/053 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPODOC and A61B 5/053J and keywords: resistance and values and spread and similar terms.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5807272 A (KUN et al.) 15 September 1998 Column 5 line 22 to column 12 line 24	1-3,5,6,10-13, 18,21,22,28-36
Y		4,7,23-27
X	WO 2001/067098 A1 (BTG INTERNATIONAL LTD) 13 September 2001 Page 11 line 15 to page 16 line 21	1-3,5,6,8-13 18,22,28-35
Y	WO 2008/138062 A1 (IMPEDIMED LIMITED) 20 November 2008 Claims 27 to 34, figures 6A to 7B	4,7,23-27

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

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"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 January 2011	18 JAN 2011
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. +61 2 6283 7999	Authorized officer **DAVID MELHUISH** AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No : +61 2 6283 2426

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU2010/001399

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2006/0293609 A1 (STAHMANN et al.) 28 December 2006 Whole document	
A	WO 2007/041783 A1 (IMPEDANCE CARDIOLOGY SYSTEMS, INC) 19 April 2007 Whole document	
A	US 5086781 A (BOOKSPAN) 11 February 1992 Whole document	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/AU2010/001399

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	5807272	NONE					
WO	0167098	AU	37555/01	CA	2401508	EP	1259806
		US	2003105411				
WO	2008138062	AU	2008251033	CA	2686883	EP	2155058
US	2006293609	NONE					
WO	2007041783	AU	2006301927	CA	2625631	EP	1948017
		US	2009043222				
US	5086781	NONE					

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX